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TITLE: Metabolizing Enzyme Polymorphisms and Prognosis Among Women Treated for Breast Cancer

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13. ABSTRACT ***(Maximum 200 Words)***

This study will use archived tissue and data to examine survival of women treated for breast cancer in relation to inherited polymorphisms of drug metabolizing enzymes. During the first year of funding, we have completed compilation of tumor registry data for eligible subjects (Task 1 of the approved statement of work). We have also completed study start-up tasks, including IRB review, hiring study staff, creating data collection forms, establishing a study database, and training study staff on data collection procedures. Collection of tissue samples (Task 2 of the approved statement of work) has begun. Activities currently in progress include obtaining pathology slides and blocks, review of slides by the study pathologist, and abstracting information from pathology reports into the study database. As described in the statement of work, data collection tasks will continue into years 2 and 3, so no reportable scientific results are available at the end of year 1.

14. SUBJECT TERMS
Breast cancer, GSTP1, GSTA1, DNA

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Table of Contents

INTRODUCTION

Despite the favorable prognosis for women treated for breast cancer, in some instances cancer will recur. Host factors may explain some differences in outcomes of treatment. Variability in enzyme activities could be a factor influencing sensitivity of cells to cancer treatment. Common polymorphisms occur in several genes encoding drug metabolizing enzymes, and the variant alleles affect enzyme activities. Glutathione *S*-transferase (GST) A1 and GSTP1 enzymes catalyze inactivating glutathionyl conjugation reactions of chemotherapeutics including cyclophosphamide. The GSTA1*B variant reduces expression of GSTA1, while a GSTP1 Val^{105} variant reduces specific activity toward alkylating agents, so these polymorphisms may improve treatment effect by reducing removal of the drug. Data from a pilot study indicate that among women treated for breast cancer, those who are homozygous for GSTP1 Val^{105} or GSTA1*B have improved overall survival. In the present study we will investigate whether presence of inherited variant alleles affecting activity of metabolizing enzymes affect overall survival or time to recurrence outcomes, and whether these associations are independent of other prognostic factors. The study will be a retrospective study of women (n=700) receiving first course of therapy for invasive, primary breast cancer, indentified through a hospital tumor registry. Information on vital status and recurrence will be obtained from registry follow-up data. We will determine genotypes using DNA extracted from normal tissue from archived surgical blocks. We will assess other prognostic markers in tumor tissue by immunohistochemistry. We will use survival analysis methods, taking into account other prognostic factors, to evaluate associations between genotypes and recurrence and overall survival.

BODY

This study will use archived tissue and data to examine survival of women treated for breast cancer in relation to inherited polymorphisms of drug metabolizing enzymes. The Statement of Work identified five tasks, as follows:

Task 1. Compilation of Data for Eligible Subjects, Months 1-3

Task 2. Archived Tissue Specimens Obtained, Months 4-24

Task 3. DNA Extraction and Genotyping, Months 6-30

Task 4. Immunohistochemistry, Months 6-30

Task 5. Data Analysis and Report Writing, Months 18-36

During the first year of funding, we have completed Task 1, compilation of tumor registry data for eligible subjects. We have also completed the following study start-up activities: IRB review and approval; hiring study staff; creating data collection forms for pathology report abstraction and pathological review of each case for eligibility; establishing a database for entering abstracted, unidentified data and tracking specimen status; training study staff on data collection procedures. Task 2, collection of tissue samples, is underway. Activities a. through f. specified under Task 2 are currently in progress including obtaining pathology slides and blocks, review of slides by the study pathologist, and abstracting information from pathology reports into the study database. Samples are being prepared to carry out laboratory assays, Tasks 3 and 4, during years 2 and 3.

KEY RESEARCH ACCOMPLISHMENTS

Data collection activities have been initiated and are proceeding. As described in the Statement of Work, data collection tasks will continue into years 2 and 3, so no reportable scientific results are available at the end of year 1. The PI presented a poster describing study methods and rationale at the "Era of Hope" Department of Defense Breast Cancer Research Program Meeting, Orlando, Florida, September 26-28, 2002.

REPORTABLE OUTCOMES

Abstract

Sweeney C, Gulbahce HE, Coles BF. Metabolizing enzyme polymorphisms and prognosis among women treated for breast cancer. "Era of Hope" Department of Defense Breast Cancer Research Program Meeting, Orlando, FL, September 26-28, 2002.

CONCLUSIONS

This study will use archived tissue and data to examine survival of women treated for breast cancer in relation to inherited polymorphisms of drug metabolizing enzymes. Data collection activities have been initiated and are proceeding. As described in the Statement of Work, data collection tasks will continue into years 2 and 3, so no reportable scientific results are available at the end of year 1.

REFERENCES

N/A

APPENDICES

N/A